Cancer of the Pancreas, Gall Bladder and Liver

VICTOR RICHARDS, M.D., San Francisco

MODERN TREATMENT of tumors of the pancreas, gall bladder and liver was pioneered by Whipple with the introduction in 1935 of the new and radical operation, pancreatico-duodenectomy. At first operative mortality was high, but by 1945 radical operation for carcinoma of the pancreas, liver or biliary tree was a common, standard, reasonably-safe procedure. Indeed, a strong tendency existed to resect any and all movable tumors within the pancreas or liver, leading to the ingenious development of techniques for the bridging of defects in the portal vein occasioned by surgical trauma, and dramatic resections of the right or left lobes of the liver. Indeed, technique often triumphed over judgment and the operating surgeon would labor for hours only to find himself within a few millimeters of cancerous tissue in crucial areas, yet unreasonably radical in the removal of vital organs in areas far removed from the neoplastic process. Results from these procedures were oftentimes unsatisfactory from the standpoint of comfort, palliation and survival. An occasional patient, however, greatly benefited for a long period from a radical surgical procedure, and in the past few years more realistic and effective approaches to treatment have been elucidated. It is particularly appropriate at this time, approximately a quarter of a century after the classic report of Whipple, to review the current status of tumors of the pancreas, bile passages and liver.

TUMORS OF THE PANCREAS

Classification

A simple classification of pancreatic tumors which can be correlated with clinical findings and give a basis for comparisons of treatment is shown in Table 1.

Incidence

Cancer of the pancreas affects patients in the middle and later years of life. It accounts for about 1 to 2 per cent of all malignant lesions and is four times as common in males as females. No causative factors are known. It is most commonly seen in natives of Uganda (South Africa), and may appear more often in diabetic than in non-diabetic patients.

General Clinical Symptoms

Jaundice, pain and loss of weight are the classical clinical features of cancer of the pancreas. Cancers of the head and peri-ampullary region produce jaundice almost invariably. Cancers of the body and tail of the pancreas are associated with pain and loss of weight as the predominant clinical features. Loss of weight, asthenia, impaired or sluggish digestion, gaseous distention and "boring" abdominal pain, often radiating to the left flank and the back, are common. Two additional symptoms and signs are worthy of special mention: (1) unexplained venous thrombosis or thrombophlebitis, and (2) unexplained chronic anemia with loss of weight from mild but continued gastrointestinal bleeding. Steatorrhea from loss of pancreatic enzymes in the bowel is rare, but diarrhea occurs in about one-third of the cases.

The islet cell tumors of the pancreas and ulcerogenic tumors of the pancreas and duodenum present special clinical features which will be discussed separately.

Metastasis occurs to the regional lymph nodes around the hepato-duodenal ligament and aorta. Metastasis to the liver, ascites and supraclavicular lymph node enlargement indicate a hopeless phase of

TABLE 1.—*Classification of Pancreatic Tumors*

	Per cent located at site
Carcinoma of the head and peri-ampullary region..	70 to 75
Carcinoma of the head of the pancreas	40
Ampulla of Vater	35
Duodenum	15
Common bile duct	10
Carcinoma of the body of the pancreas and the tail	15 to 20
Islet-cell tumors of the pancreas	5 to 10
Benign adenomas	60
Carcinomas	40
Ulcerogenic tumors of pancreas or duodenum	5
Other rare benign tumors of pancreas (fibromas, lipomas, chondromas, angiomas, etc.)	<1

From the Department of Surgery, Presbyterian Medical Center, San Francisco.

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the disease. Diabetes mellitus occurs in 5 to 10 per cent of cases.

General Clinical Signs

Jaundice, progressive, persistent and unrelenting, is the classical clinical sign of pancreatic carcinoma. It is invariably present in carcinoma of the head and peri-ampullary region, with the exception of lesions of the duodenum proper. Hepatic enlargement accompanies the jaundice, but is not striking unless cholangitis is present or metastasis to the liver has occurred. The gall bladder is enlarged in all cases of neoplastic obstruction of the biliary tract, but it is palpable in only 30 per cent of cases. An enlarged non-tender gall bladder in a jaundiced patient may be taken as a reliable sign of malignant choledochal obstruction (Courvoisier's law), but no diagnostic inference is justified if the gall bladder is not palpable.

Evidences of loss of weight and chronic pain generally accompany all stages of the disease. Anemia is not uncommon. Carcinoma of the body and tail of the pancreas tend to compress the superior mesenteric or splenic veins, and gastrointestinal bleeding, splenic vein thrombosis and splenomegaly occur particularly with cancers in these areas. Spontaneous venous thrombosis in the legs with unexplained loss of weight and anemia should arouse clinical suspicion of cancer of the body or tail of the pancreas. Liver enlargement of a nodular character, ascites and supraclavicular lymph node enlargement are signs of metastatic disease.

The clinical signs unfortunately appear rather late in the disease. The abundance of pancreatic acinar tissue and the access of pancreatic enzymes to the intestinal tract through multiple ductile channels mask the signs of pancreatic insufficiency. Jaundice and acholic stools appear long before the greasy, bulky and pultaceous stools of pancreatic insufficiency. Jaundice, abdominal pain and loss of weight are the first clinical signs to appear, but again are not early manifestations in the total history of the disease.

Laboratory Data

Abnormal laboratory findings also appear rather late in the course of the disease, and characteristically are those of progressive and persistent obstructive or regurgitant jaundice. Bilirubinemia, choluria and clay-colored putty-like stools are typical of obstructive jaundice. Disturbed liver function tests follow, and the alkaline phosphatase may be elevated, the thymol turbidity and cephalin flocculation tests indicative of varying degrees of liver damage. Since bile salts are necessary for the absorption of vitamin K, hypoprothrombinemia develops commonly after prolonged biliary obstruction.

Recently, efforts have been made to diagnose pancreatic cancers earlier by special laboratory studies, but unfortunately the functional capacity of the remaining pancreatic cells makes these diagnostic studies unreliable. The special studies include: (1) blood sugar determination, glucose tolerance tests or determination of glycosuria (which prove abnormal in about 40 per cent of the cases); (2) serum levels of pancreatic enzymes such as trypsin, trypsin-inhibitor, amylase, plasma carotene, plasma antithrombin and paritol-C and serum glutamic oxalacetic transaminase (SGO-T); (3) hepatic function tests, such as determination of serum alkaline phosphatase and serum bilirubin levels, and the measurement of retention of rose Bengal dye or bromsulphthalein dye by the liver.

Combined Cytologic and Secretory Diagnosis of Pancreatic and Biliary Carcinoma

Duodenal intubation can be done quickly and easily, and the hope is that a combined study of duodenal aspirate by cytologic techniques and analysis of duodenal enzymes will lead to an early and accurate diagnosis of pancreatic cancers. Unfortunately, the tests are reliable in only about 50 per cent of cases. A positive result of exfoliative cytology is significant, but not a negative result. The volume of pancreatic secretion may be diminished from duct obstruction and duodenal enzymes may be reduced, particularly after secretin administration to stimulate pancreatic secretion into the duodenum, but the diminished volume of pancreatic secretion and decreased bicarbonate and enzyme content are not highly reliable diagnostic adjuncts. The clinical features of the disease and its common laboratory abnormalities generally indicate the need for exploratory laparotomy without reliance on special studies.

Radiologic Examination

Abnormal radiologic findings will be present in either the duodenal loop or stomach in approximately 50 per cent of the cases. Widening of the duodenal loop, anterior displacement of the stomach, disturbed mucosal patterns in the duodenal loop, and the "reverse 3 sign" or "epsilon sign" in the second portion of the duodenum are the roentgen signs usually detected. Duodenitis, pancreatitis and pancreatic cysts may mimic pancreatic carcinoma in x-ray studies. Yet gastrointestinal films should always be taken.

Cholecystography and intravenous cholangiography are generally of little or no avail in the diagnosis of pancreatic cancers. Visualization is normal in the absence of jaundice and absent in the presence of clinical jaundice. Percutaneous transhepatic cholangiography may be helpful when simpler methods fail to distinguish between obstructive and non-ob-

TABLE 2.—*Summary of Clinical Features and Laboratory Findings in Cancer of the Pancreas*

	Cancer of Ampulla	Cancer of Bile Ducts	Cancer of Head	Cancer of Body and Tail
Pain	present 40% mild	present 60% mild	present 85% moderate	present 100% severe
Jaundice	early progressive	early progressive	variable progressive	absent or late mild
Loss of weight prior to jaundice	minimal	minimal	mild	pronounced 10 to 40 lb.
Fever, chills	20%	10%	none	low-grade chronic
Hepatomegaly	none	rare	moderate	moderate to huge, if metastases
Palpable gall bladder	40%	30%	40%	0%
Splenomegaly	none	none	none	rare
Bile in stools	absent 80%	absent 90%	absent 100%	present
Occult blood in stools	50%	10%	10%	rare until late

structive jaundice, and probably deserves wider use; but it is not always successful and occasionally results in serious bile peritonitis.

Splenoportography and retroperitoneal pneumopancreatography are rarely of value in the diagnosis of pancreatic tumors. By the time these procedures might be helpful, exploratory laparotomy is already indicated.

Differential Diagnosis

When the patient is not jaundiced, diagnosis is difficult and in the initial stages the patient is often considered psychoneurotic. Persistent pain and progressive loss of weight with negative radiologic findings of the alimentary, biliary and renal tracts should raise suspicion of pancreatic cancer. Duodenal aspiration with search for neoplastic cells in the cellular sediment may yield a proper diagnosis.

In jaundiced patients, other causes of obstructive jaundice, such as common duct stone and stricture, and all causes of hepatocellular or hepatocanalicular jaundice must be considered. A palpable gall bladder strongly suggests neoplastic obstruction of the common duct, but it must be emphasized that the combination of jaundice and a palpable gall bladder occur in only 30 per cent of patients with resectable pancreatic tumors. The differential diagnosis of jaundice is notoriously difficult, and in many cases the issue can only be settled by surgical exploration of the abdomen. Needle biopsy of the liver may be used in an effort to distinguish surgical (obstructive) from non-surgical (hepatocellular or hepatocanalicular) jaundice, but it carries a mild risk from bleeding due to the associated hypoprothrombinemia and may not yield enough tissue for the average pathologist.

Exploratory laparotomy is oftentimes necessary to establish a definite diagnosis and to initiate adequate therapy. It should be advised within three weeks or at the most four weeks after the onset of jaundice, if the cause of the jaundice is not entirely clear after that period of observation and treatment.

The clinical features and laboratory findings in cancer of the pancreas are summarized in Table 2.

The Role of Exploratory Laparotomy

Laparotomy should be considered in any case of jaundice in which the diagnosis cannot be clearly established within three weeks of onset in a patient of middle years or older. Laparotomy is strongly indicated in all cases of jaundice in which diagnostic and therapeutic measures have not succeeded after four weeks of jaundice.

Exploratory laparotomy should be considered as a diagnostic adjunct in patients of middle years and beyond who have unexplained abdominal pain and weight loss that is progressive with negative radiological studies of the alimentary, biliary and renal passages. Hypercalcemia hyperlipemia, porphyrin disease, macroglobulinemia and metastatic malignant disease should be carefully excluded before laparotomy, however.

Differential Diagnosis During Abdominal Exploration

The results from radical pancreatic resection are good in carcinomas of the ampulla of Vater, bile duct carcinoma and duodenal carcinomas. They are much poorer in carcinoma of the head of the pancreas. A good result entails five-year survival of 35 to 40 per cent; a poor result a five-year survival of 5 to 7 per cent. It is important therefore, to distinguish the nature of the pancreatic carcinoma at the time of laparotomy. Radical pancreatico-duodenectomy is warranted for carcinomas of the ampulla of Vater, bile duct or duodenum; but, radical resection in cases of carcinoma of the head and body of the pancreas should be reserved for early, favorable and truly resectable cases in which all visible and palpable tumor can be removed with a safe margin around all areas of the tumor. Involvement of regional lymph nodes and adherence to the portal or splenic vein are factors against favorable results even though resection is technically feasible. Extending operability by resection of the portal vein or violating sound precepts of cancer surgery merely to remove a tumor inadequately and incompletely is ill-advised, for life is not prolonged and better palliation can be achieved by simpler procedures, such as cholecystoduodenostomy, cholecystogastrostomy or

cholecystoenterostomy, which reestablish the flow of bile into the intestinal tract.

At laparotomy the head of the pancreas and duodenum are first mobilized, permitting careful palpation on all aspects of the structures. Primary carcinoma of the head of the pancreas is characterized by a dilated common duct which is thin-walled and bluish. The gall bladder is distended, no stones are palpable in it or in the common duct, and a tumor mass can be felt in the vicinity of the head of the pancreas. The margins of the tumor are indistinct but immediately beyond the medial limit of the tumor the duct of Wirsung is palpable in the neck and proximal body of the gland. The dilatation of the duct of Wirsung is present in 80 per cent of the cases of carcinoma of the head of the pancreas, and the dual dilatation of the thin, distended common duct and dilated duct of Wirsung is pathognomonic of carcinoma of the head of the pancreas, a lesion with poor prognosis even if radical pancreaticoduodenectomy is technically possible. Involvement of the portal vein, extension to regional lymph nodes and spread to peri-pancreatic structures denote inoperability, and bile flow should be restored to the intestinal tract by anastomosis of the gall bladder or common duct to either the stomach, the duodenum or the jejunum. The average survival after palliative operation is approximately 11 months, but equals the survival after inadequate radical pancreatico-duodenectomy yet entails considerably lower morbidity and mortality.

Carcinoma of the ampulla of Vater produces a dilated thin-walled common duct, but only in 20 per cent of the cases is the duct of Wirsung obstructed with a palpable dilatation of this pancreatic duct. Furthermore, after mobilization the tumor can be felt along the medial wall of the duodenum rather than in the head of the pancreas. The extension along the medial wall of the duodenum produces a marble-like hardening along the course of the duodenal lumen medially.

Carcinomas of the bile duct, whether located just above the duodenum or in the intrapancreatic portion of the distal common bile duct, produce the same extrahepatic biliary tract signs of a dilated thin-walled common duct, but these tumors do not obstruct the duct of Wirsung, nor do they produce a mass which projects into the duodenal lumen or infiltrates along the medial duodenal wall. A dilated gall bladder, the absence of stones within the biliary tree with a thin-walled dilated common duct, and a tumor just above the ampulla of Vater not obstructing the duct of Wirsung complete the gross pathological picture of carcinoma of the bile duct.

Carcinomas of the duodenum are rarely difficult to diagnose, for they encircle the duodenum and often have a large central ulceration. If large, they may obstruct both the common bile duct and the duct of Wirsung, but the tumor can be palpated in the duodenal lumen rather than in the pancreatic head.

Chronic pancreatitis may simulate carcinoma of the pancreas, but generally in pancreatitis the common duct is not greatly dilated, jaundice is mild, and the common duct and peritoneum overlying the duct are pale and thickened, not thin and bluish. Indeed, identification of the common duct may be difficult because of the associated inflammatory process around the head of the pancreas.

A stone impacted in the distal common duct produces edema and induration in the head of the pancreas. The gall bladder is generally not distended and most often other stones are palpable within it or the common duct. The duct of Wirsung is not obstructed unless a large hard inflammatory mass has developed. Rarely, peptic ulceration of a benign type occurs at the level of the ampulla of Vater or distal to it, and is not often confused with carcinoma.

The Role of Biopsy in Diagnosis

Biopsy of the pancreas *per se* is generally an unsatisfactory procedure. The use of the Silvermann needle is recommended by some investigators, but generally it is unsatisfactory. Direct biopsy of the pancreas carries some danger from injury to the pancreatic ductile system with subsequent pancreatitis, and it, too, is difficult and unsatisfactory. It carries the risk also of spreading the tumor.

Lesions of the ampulla of Vater and duodenum are best visualized and biopsy carried out directly through a duodenotomy incision. Lesions of the distal common duct are best approached for biopsy through a transverse incision in the common duct at the level of future transection of the duct in the event of a pancreatic resection. From within the bile duct a small scoop can obtain a biopsy specimen suitable for diagnosis and also eliminate the possibility of a stone being impacted in the distal ampulla. The combined exploration from the common duct above and from within the duodenum below offers the best approach to biopsy of resectable carcinomas. The carcinomas of the head of the pancreas are best recognized by the gross findings described above, and if the lesion is operable the surgeon may proceed with pancreatico-duodenectomy without preliminary biopsy. Statistically, errors will be made on this basis in approximately 3 per cent of the cases, that is, the lesion in the head of the pancreas will be inflammatory rather than neoplastic.

Contraindications to Radical Operation

Four findings contraindicate radical pancreaticoduodenal resection: (1) distant metastasis, (2) local

spread beyond the limits of a resection with adequate margins around the tumor, (3) involvement of the superior mesenteric or splenic vessels, and (4) invasion and involvement of the portal vein.

The prognosis in cases of carcinoma of the ampulla of Vater, malignant tumors arising in the intrapancreatic portion of the common bile duct and carcinomas of the duodenum is more favorable, and pancreatico-duodenectomy is the preferred treatment in this group. Carcinoma of the head of the pancreas has a much poorer prognosis, and resection should be reserved for truly operable situations.

Palliative Operative Procedures

Carcinomas of the pancreas obstruct first the biliary and pancreatic duct, and later the duodenum. Palliative procedures, therefore, include anastomosis of either the gall bladder or dilated common bile duct to either the stomach, the duodenum or the upper jejunum as the prime procedure. Oftentimes a dilated duct of Wirsung can also be joined to a jejunal loop in a side-to-side fashion to relieve pancreatic duct obstruction, but this is not as important as relief of biliary obstruction. If the size of the tumor suggests duodenal obstruction will soon follow, gastro-enterostomy is indicated, and the cholecysto-anastomosis or choldedocho-anastomosis should not be made to the duodenum but rather to the stomach or jejunum.

Radical, Possibly Curative, Operative Procedures

Resection of the distal half of the stomach, all the duodenal loop including the head of the pancreas and the regional lymph nodes constitutes a pancreatico-duodenectomy, a definitive resection of the carcinoma, with a chance for cure of the cancer. Reestablishment of continuity of the biliary tract to the jejunum is mandatory; gastro-jejunal anastomosis is necessary for alimentary continuity, and anastomosis of the pancreatic duct into the upper jejunum is advisable but not mandatory. The preferable sequence in anastomosis seems to be to re-implant the bile duct and pancreatic duct into the jejunum proximal to the gastro-jejunostomy, so that the gastro-jejunal anastomosis will be bathed in the alkaline bile and pancreatic juices, and regurgitant cholangitis will be less likely to occur. However, surgeons differ widely in their methods of reestablishing the flow of bile, pancreatic and gastric juices into the jejunum. Indeed, many surgeons prefer not to reanastomose the divided pancreatic duct at all, saying that the incidence of pancreatic fistula is reduced postoperatively by ligation of the pancreatic duct and that absence of pancreatic enzymes in the bowel is not disturbing. I prefer to join the divided end of the pancreas to the divided end of the jejunum, leaving a small polyethylene cannula in the pancreatic duct, then re-implant the end of the common duct into the side of the jejunum a few centimeters distal to the pancreatic anastomosis, and follow with a gastro-enterostomy some 20 centimeters or more distal to the choledocho-jejunal anastomosis. The incidence of postoperative gastro-jejunal ulcer seems more related to the inadequate gastrectomy than to the absence of alkaline bile and pancreatic juices at the anastomotic site. Recently, more extensive gastric resection has been advocated with the pancreatico-duodenectomy in an effort to prevent postoperative gastro-jejunal ulceration; also, vagotomy has been added to the operation.

Complications of Radical Pancreatico-Duodenectomy

Pancreatic fistula formation or bile fistula formation constitute the immediate posoperative hazards surgically. Some surgeons prefer to ligate the divided pancreatic duct and oversew the end of the pancreas rather than to re-do the anastomosis of the pancreas to the bowel in an effort to avoid this complication. The incidence of diabetes mellitus, and pancreatic acinar insufficiency postoperatively may be increased, but only slightly, by failure to reestablish anastomosis of the pancreas to the bowel.

The later surgical complications, aside from recurrence of cancer include diabetes mellitus, malabsorption syndromes with pancreatic acinar insufficiency, and jejunal ulceration at the gastro-jejunal stoma.

Diabetes mellitus is not severe. The pancreatic acinar insufficiency may be improved by the ingestion of viokase, a pancreatic supplement, 0.6 gm every 2 hours from 7 a.m. to 7 p.m., and the jejunal ulceration may be prevented by more extensive gastric resection at the time of pancreatico-duodenectomy or by accompanying vagotomy.

Failure to cure the pancreatic cancer is the major postoperative complication.

Mortality

Radical pancreatico-duodenectomy carries a mortality rate of 12 to 20 per cent in best surgical centers. Palliative operation with relief of biliary obstruction carries a mortality rate of less than 5 per cent. Efforts have been made to reduce the mortality from radical operation by performing two-stage procedures, relieving the jaundice at the first stage by cholecysto-jejunostomy or choledocho-jejunostomy, and performing the resection of the tumor at the second stage. This has not proved successful, and the majority of surgeons now favor a one-stage procedure except in very poor risk patients.

The causes of death after pancreatic resection are, in the order of frequency: Fistula formation with bile or pancreatic peritonitis, hemorrhage related to anastomotic leaks, renal failure, coronary and cere-

bral lesions, or liver necrosis. It seems unlikely the operative mortality will be reduced below 10 to 15 per cent in pancreatic resection.

Results

If not treated, patients with pancreatic cancer generally die within two or three months after the onset of jaundice.

The average survival after palliative operation for cancer of the head of the pancreas is 11 to 14 months.

Pancreatico-duodenectomy yields the following five-year survival results: (1) carcinoma of the head of the pancreas—5 to 8 per cent; (2) cancer of the ampulla of Vater—35 per cent to 40 per cent; (3) cancer of the distal bile ducts—35 per cent to 40 per cent, and (4) cancer of the duodenum—40 per cent. Clearly, for cancers of the head of the pancreas, radical operation should be carried out only if the lesion is readily removable, but the range of operability is broader in cancers of the ampulla, duodenum and distal bile ducts.

A search for methods of therapy more successful than surgical operation is strongly indicated. However, irradiation, chemotherapy and intrapancreatic injections of colloidal isotopes have not proved satisfactory, and at present offer less palliation than operation and less likelihood of more enduring arrest of the cancer. Cancers of the body and tail of the pancreas are unfortunately rarely operable, but again should be approached surgically. Total pancreatectomy can be carried out, if necessary, with a mortality rate of approximately 35 to 40 per cent. Diabetes mellitus can be controlled after total pancreatectomy, surprisingly with about 20 to 40 units of insulin daily, and the disturbances in carbohydrate, fat and liver metabolism can be compatible with survival under diligent medical treatment with diet, pancreatic acinar substitutes such as viokase, and possibly lipocaic, another possible pancreatic hormone. This heroic procedure, however, should be reserved for the very rare truly operable case.

ISLET-CELL TUMORS OF THE PANCREAS

It is beyond the scope of this review to discuss in detail islet-cell tumors of the pancreas, but a brief note must be made that 25 to 30 per cent of such tumors may be malignant and may metastasize. They tend to occur in persons under 50, and oftener in males than females.

Pathological Classification

Islet-cell tumors may be classified on the basis of clinical and pathological features as follows:

1. Adenomas of the islet-cells without hypoglycemia.
2. Adenomas of the islet-cells with hyperinsulinism.
3. Metastasizing carcinomas of islet-cells without hypoglycemia.
4. Metastasizing carcinomas of islet-cells with hypoglycemia.
5. Borderline malignant islet-cell tumors with or without hypoglycemia.

Clinical Features

The generally accepted criteria of functioning islet-cell tumors consist of the so-called Whipple's triad:

1. Spontaneous hypoglycemia accompanied by central nervous, psychiatric or vasomotor system symptoms—fainting, sweating, convulsions, collapse, etc. These attacks come during periods of exertion or after fasting.
2. Blood sugar persistently less than 50 mg per 100 ml during an attack or after a period of fasting.
3. Relief of symptoms by the oral or intravenous administration of glucose.

The other causes of hypoglycemia must be eliminated by appropriate physical signs and laboratory examinations. These include hepatic disease, pituitary hypofunction, adrenocortical hypofunction, and functional hypoglycemia related to renal glycosuria, overwork, diet, pregnancy and lactation.

The malignant tumors not associated with hypoglycemia present as an abdominal mass with weight loss. Diagnosis is established by laparotomy.

Differential Diagnosis

Liver function tests, adrenal function tests, including eosinophil counts, 17 ketosteroid and 11 oxysteroid determinations, ACTH stimulation and decadron suppression tests, x-ray films of the skull and visual field studies rule out hepatic, adrenal and pituitary causes of hypoglycemia.

Adrenal tolerance, glucose tolerance and insulin tolerance tests are valuable but not infallible. Recently, leucine and tolbutamide (Orinase) have been shown to produce a prolonged and profound hypoglycemia in patients with insulinomas but not in patients with other forms of hypoglycemia. The leucine is given orally in a dose of 150 mg per kg of body weight; the tolbutamide is given intravenously in a dose of 1 gram.

Hypoglycemia is occasionally found in certain retroperitoneal tumors.

Treatment

Surgical exploration is indicated. The insulinomas are removed if easily identified. If an easily resectable tumor cannot be found, the tail and body of

the pancreas can be resected, for these tumors are often small. If the resected specimen fails to show a tumor and hyperinsulinism persists, total pancreatectomy may be necessary at a second operative procedure. Extrapancreatic sites of insulinomas have been reported, and should be searched for in the usual sites of pancreatic heterotopia. Similarly, retroperitoneal tumors should be excluded at the time of laparotomy.

The non-insulin producing tumors should be resected as for carcinoma of the pancreas in general.

ULCEROGENIC TUMORS OF PANCREAS AND DUODENUM

Zollinger and Ellison in 1955 described the association of non-insulin producing (non-beta cell) tumors of the pancreas and progressive peptic ulceration. These tumors are rare in either the pancreas or duodenum. They should be mentioned for they behave like malignant, metastasizing but small pancreatic cancers, and they require special treatment, preferably on the stomach. The lesions may be multiple, benign adenomas or malignant and metastasizing carcinomas of small size in either the pancreas or duodenum. They look like insulinomas but are non-beta cell in origin.

Clinical Features

The clinical features are those of malignant recurrent peptic ulcer disease. The ulcers are often located atypically in the jejunum or second and third portion of the duodenum. They commonly appear after gastric operations. Hypersecretion of gastric acid invariably accompanies these lesions, presumably from the elaboration of a gastrin-like substance from them. The 12-hour basal gastric secretion often exceeds 100 mEq of hydrochloric acid and the volume of gastric secretion produced is large. Diarrhea is a common associated clinical feature of these tumors.

Treatment

Total gastrectomy seems the treatment of choice, for these tumors are often multiple and hard to remove locally. Recurrent ulceration of the stomach follows even extensive subtotal gastrectomy, with or without vagotomy. The localized adenomas within the duodenum may be resected locally. The malignant adenomas in the duodenum require pancreaticoduodenectomy. In this regard the duodenal ulcerogenic tumors behave differently from the pancreatic ulcerogenic tumors, for the latter rarely respond to local removal of the ulcerogenic foci.

CARCINOMA OF THE GALL BLADDER

Carcinoma of the gall bladder is extremely rare in the absence of gall stones. It is felt to occur in about 2 per cent of all patients having gall stones if the stones go untreated for a number of years. Women are more affected than men, and it is rapidly fatal once it has spread beyond the confines of the gall bladder proper.

Clinical Features

Pain, jaundice, and recent loss of weight comprise the clinical picture in the majority of cases. It should be particularly suspected in (1) patients in the older age group whose biliary tract symptoms are less than six months' duration, (2) patients with a long history of biliary tract disease with a sudden change of symptoms or increase in severity of attacks. In the majority of patients, however, it is an incidental discovery at the time of laparotomy.

Treatment

Cholecystectomy is the treatment of choice. If the carcinoma has spread beyond the gall bladder proper, the prognosis is extremely poor and the majority of patients are dead within a year. There is about a 5 per cent five-year survival rate in this disease.

Prevention is the treatment of choice. This requires cholecystectomy early in the course of the disease in an otherwise healthy good risk patient with cholelithiasis. Fortunately, repeated bouts of biliary colic and repeated bouts of cholecystitis generally bring the patient to accept operation for more urgent and common reasons.

BENIGN TUMORS OF THE GALL BLADDER

Adenomas, papillomas and adenomyomas are the commonest benign tumors of the gall bladder. Noninvasive carcinomas and fibroadenomas are much less frequent. The clinical manifestations of these lesions are not typical, but they are commonly associated with gall stones and produce symptoms accordingly. Gaseous indigestion and vague upper abdominal pains may lead to cholecystographic examination and disclosure of the lesion. The cholecystogram shows a fixed radiolucent defect.

Treatment

No definite proof exists that these lesions are premalignant. Nevertheless, the consensus of surgical opinion favors cholecystectomy as the treatment of choice when there is no contraindication to the operative procedure.

NEOPLASMS OF THE LIVER

The left lobe of the liver can be easily and readily resected. The right lobe of the liver can be resected

with great difficulty and high mortality as an occasional technical feat requiring skill and refined judgment. A brief classification of tumors of the liver is, therefore, warranted, although surgical removal of tumors of the liver is rare.

Classification

Benign tumors—Adenomas of liver cells or bile ducts; hemangiomas, lymphangiomas, myomas, teratomas.

Malignant tumors—Primary: carcinoma of liver cell (hepatoma), bile duct (cholangioma) or mixed-cell types; sarcomas. *Secondary*: any and all metastatic tumors.

Clinical Features

There are no characteristic symptoms or signs. The symptoms are due to loss of weight, size of the lesion, compression of contiguous structures, etc. Metastatic tumors are by far the commoner group. Cirrhosis is commonly associated with a hepatoma or cholangioma as a primary disease.

Treatment

Easily resectable tumors are best treated by surgical methods. The left lobe can be resected easily, if necessary. Resection of the right lobe is rarely indicated.

Presbyterian Medical Center, Clay and Webster streets, San Francisco, California 94115.